# United States Patent 1191

Barberich et al.

[11] Patent Number:

[45] Date of Patent: Aug. 20, 1996

### [54] METHOD FOR TREATING ASTRIMA USING OPTICALLY PURE R(-) ALBUTEROL

- [75] Inventor: Thundby J. Barberich, Concord, James W. Young, Still River, both of
- [73] Assigner Sepracus, Inc. Mariborough, Mass.
- [21] Appl. No.: 335,480
- [22] Filed: Nov. 7, 1994

### Related U.S. Application Data

Confination of Ser No. 163-581, Dec 7, 1993, Par. No. 5302-753, Which is sensitivation of Ser No. 196-723, has 9, 1992, thendened, which is a continuous of Ser No. 461,202, jun. 3, 1991, shundooed.

[31] Int.	CL.			A61K 31/135
[52] U.S.	CL	in district	514	/649, 514/826
[58] Fleh	d of Seme	<b></b>		514/649, 826

References Cited

U.S. PATHYT DECUMENTS 5,362,755 11/1994 Batterich et al.

FOREIGN PATENT DOCUMENTS

2235603 76992 Univel Kleybro .

### OTHER PUBLICATIONS

Tam et al. "Stemosticutive Disposition of Salbulannol Enin-forners ......" Clin. Chem. 33, 1026 (1987). British et al. "Semo observations on the B-adrenoceptor agonist ....." Br. J. Pharmac. 48, 144–147 (1973).

Hartley et al. "Absolute Configuration of the Optical Isomers of Salbutanol" J. Med. Chem. 12, 995 (1971). Hawkinset al. "Relative Potency of (-) and (1) Salhutanol on Guinea Fig. ... "J. Med. Chem. 18, 856-857 (1973). Buchner et al. "Studies on the Effects of Busilianess of Soteranol, Timetoquinol ..." J. Phane. Eq. Ther. 189, 616-625 (1974). 616-625 (1974).

Passowicz-Muszyńska R. "Effect on beta adrenerpie recep-

Passowici-Muszynska R. "Effect on best adveningly receptors of (achyphylaxis..." Index Medicus 91:164287 (1990). Parwels "Effect of continueteroids on the action of sympathonium its" index Medicus 86:051970 (1983).

Chapman et al. "An anomalous effect of salariamed in sensitive gither pigs" Brit. J. Pharmacol 99, 66P (1990).

Marky et al. "Effects of (+) and member salariamed on airway responses in the gather pigs" Brit. J. Pharmacol 104, 295P (1991).

Chapman et al. "Recentle ministra at 1001 of wereigning symptoms? Active grantiumers ... "Tips 13, 231–232 (1992).

Mulitari et al. "Comparison of acute broashodilator effects of oral salbutantol, ..., " Chem. About 89: 123259ta (1978).

Primary Examinet—Responsed Healey, III Attorney, Agent, or From—Health & Rothenberg, P.C.

### ABSURACZ [57]

The optically pure R(-) isomer of albaterol, which is anostantially thee of the S(+) isomer, it is potent branchoffisor for reliating the symptoms associated with authors in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albaterol for breating assisms while minimizing the side effects associated with albaterol.

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# METROD FOR TREATING ASTRIMA USING OPTICALLY PURE R(-) ALBUTEROL

# CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Set. No. 08/163-581, filed Dec. 7, 1993 and now U.S. Fat. No. 5,362,755, which was a continuation of application Set. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Set. No. 07/461,262 filed Jan. 5, 1990, now abandoned.

# BACKGROUND

Albaterol is a drog teclosping to the general class of 15 bets advenerate compounds. The prime action of bets altractic charges thugs is to attending adeay! cycline, the curyme which estalyzes the formation of cyclin 7.3-alcasome monophosphate (ALP) from advances triphosphate (ALP). The cyclic AMP formed mediates the cellular responses. 24 Albaterol acts selectively not bets, advenerate receptions to relax amount muscle hissoe, for complex in the impachial system. Albaterol is mest commonly used to heat broughted system associated with authors and is the active component in well-known commercial broachodilisters such as Proym. 25 in and Ventolia.

The form in which albuterol is presently used is a recensive mixture. That is, it is a mixture of optical isomers, called ensurionness. Ensurionness are structurally identical compounds which differ only in that one isomer is a mixture so image of the other and the mixture images caused be superimposed. This phenomenon is known as chirality. Most histogical molecules exist as ensurioness and exhibit chirality. Although structurally literatess, causiumers can have profoundly different effects in biological systems one ensuring the mixture may have a specific biological activity while the other causiumers are no biological activity at all, or may have an entirely different form of biological activity.

### SUMMARY OF THE INVENTION

The present invention relates to a method of freating branchial disorders, such as authors, in an individual, by administrating to the individual an amount of optically pure R(-) altered which is active in broachial itsess sufficient to reduce branchial spaces associated with alternowl. The method is particularly useful in treating astima while minimizing side effects associated with alternowl. The method is particularly useful in treating astimas while reducing side effects, such as central nervous system stimulatory effects and cardiac mythenia. In these applications, it is an important to have a composition which is a potent branch dilator and which does not exhibit the adverse side effects of many beta advencing drugs. A composition containing the pure R(-) isomer of albeitrol is particularly useful for this application because this isomer exhibits these desired charse populations. The present method provides a safe, effective method for treating astuma while reducing anticinable side effects, for example, tremor, nervosaces, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta advencing in desirable side children, side effects such as exclamant, nervosaces and hyperimenia are reduced when the parts isomer is administrated. In addition to the above, at certain levels meeting allowered can exame tendogenic effects, which are believed to is associated with the S(s) isomer. Administrating the pure is isomer reduced with the S(s) isomer. Administrating the pure isomer reduced with the S(s) isomer.

### Z DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broughodilation activity of the R(-) constituter of albaten) to provide relief from broncitial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system simulatory effects and cardiac disorders, commonly experienced by abuterol users. In the present method, the optically pure R(-) isomer of albaterol, which is substantially fire of the S(+) coantitioner, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (a.g. relief from bronchial spanus, shortness of breath) is desired. The optically pure R(-) isomer of albaterol as tred herein refers to the lewnomancy optically pure isomer of or ((text-betylamino) methyl). A hydrocy-m-xylene-u, of-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially fire of the S(+) coantitioner" as used, herein means that the composition contains at least 90% by weight of the R(-) isomer of albaterol and 10% by weight or less of the S(+) isomer of albaterol and 10% by weight or less of the S(+) isomer. Optically pure albaterol is readily obtainable by methods known to those of shill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of silbuterol is

In the present method, the R(-) isomer of allottered is administrated to an individual who has asthma. For example, R(-) allottered is administrated to an individual after coxet of authors to rechire breathing difficulty menting from athma. In another embodiment, optically pure R(-) allottered is administrated, prophylactically, that is, before the bromphylactically, that is, before the browning of the reduce the extent to which it occurs.

In the present method, R(-) albutered can be scholalistically by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transfermally, recally or via an implement enservoir containing the drop. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emultion) will depend on the trough by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part in consideration of the individual's size, the severity of the symptoms to be treated and the result sought in general, quantities in optically pure R(-) albutered antificient to reduce the symptoms of asilma will be administered. The actual design (quantity administered at a time) and the number of aiministrations per day will depend on the mode of administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albutered given by inhalation one or more times per day will be adequate in most individuals to produce the desired broachodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to our times daily is administration, etc.

In the method of the present invention, the optically pure R(-) bromer of albuterol can be administered together with one or more other drug(s). For example, an antiauthmetic drug such as theophylline or terbutaline, or an antibistamine or sunlgesic such as aspiron, actionshophen or thoroten, can be given with or is close temperal proximity to administration of optically pure, R(-) albuterol. The two (or more) drugs (the optically pure active issues of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsale, tablet, powder, or liquid, etc. or as individual compounds. The components included in a par-

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ticular composition, is addition to optically pure albuterol and another drug or drugs, are determined priminity by the manner in which the composition is to be administered. For example, a composition to be administered in inhibitor form can include, in addition to the drug(s), a liquid camier and/or 5 propelles. A composition to be administered in tables from can include a filter (e.g., lactore), a binder (e.g., carboxymethyl cellulose, gum arabic, gelanin), an adjavani, a flavoring agent, a coloring agent and a cooling material (e.g., wax or a plasticizer). A composition to be administered in liquid 10 form can include the combination of drugs and, optionally, an empleifying agent, a flavering agent and/or a coloring

In general, according to the method of the present inven-tion, the optically pure R(-) isomer of albuterel, alone or in 15 combination with another drug(s); it administrate to an individual periodically as necessary to mosce symptoms of

The persent composition and method provide an effective treatment for asthma while minimizing the undestrable side effects associated with altonizations. These title effects include steared with altonizations of fixed title as include, steared environs system, effects, such as treatment, nervousness, shakiness, dischaess and increased appetite, and cardiac effects, such as exchement, nervousness and hyperistrations, are included when the pure issueer is administered, in addition, teratogenic effects associated with albutent are addition, teratogenic effects associated with alberterol are believed to reside in the S(+) manifemer. Thus, administering the pure R(-) isomer may reduce the teratograic potential sesociated with abuterol.

# EQUIVALENTS

Those skilled in the art will recognize, or be able to escertain, using no more than routing experimentation, many equivalents to the specific embediments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

I. A method of treating an scate attack of authors, while reducing side effects associated with the acute administration of racemic albaterol; comprising administrating to an individual suffering from an acute attack of authors a quantity of an optically pure R(-) isomer of albatard infinient to rigidit in procedulation while simultaneously reducing undestrable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(-) isomer of albuterol is greater than apparatimately 90% by

weight.

3. A method of claim 2 wherein the smoont of the R(-)

isomer of albutent is greater than 99% by weight.

4. A method of chim I comprising administrating to the adividual by inhalation from approximately 30 mag to approximately 90 mag of the R(-) isomer of albutent per Acid

approximately 90 meg of the M-) assume as account of dose.

5. A method of realing an acute attack of actimia, while reducing side effects associated with the acute administration of motivide about the computing administrating to an individual sufficient from an acute attack of asthma a quantity of an optically pair R(-) issues of allocated sufficient to result in bronchoffluidon while simulaneously reducing undestrable title effects, and at least one additional drug successful from the group constituing of innochoffluious, and histantines and analysistes.

6. A method of claim 5 wherein the scalegate is selected from the group constituing of asphin, acclauminophen and ibuptofen.

DLEV011782

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants Barberich et al.

Docket No.: 0701:027D

08/691,604

Group Art Unit: 1205

Filed: August 15, 1996.

Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)
ALBUTEROL

ARP 12/12/57

### CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mall in an envelope addressed to: Assistant Commissioner for Patents, Box Non Pee Amendment, Washington, D.C. 20231, on November 20, 1997.

Philip E. Hansen Agent for Applicants Reg. No. 32,700

Date of Signature: November 20, 1997

Assistant Commissioner for Patents
Box Non Fee Amendment
Washington, D.C. 20231

### AMENDMENT AND RESPONSE INDER 37 C R R 1 111

Dear Sir:

This is a response to an Office Action mailed August 25, 1997 (paper number 9). As response to the Action is due by November 25, 1997, this paper is timely filed.

### Amendment

Please amend the application as follows:

In the claims:

Please cancel claims 13 and 14.

Line 1 of claims 15, 16, 17 and 19, delete "13 or 14" and insert therefor -23-

PANSERS VERROU POZZÓ NES

USSN 08/691.604 Barberich et al.

The present application is a continuation of USSN 08/335,480, which included claims 1-12. All claims pending in the original application were canceled and new claims 13-23 were added in a preliminary amendment filed with the present application. Claims 13 and 14 are canceled herein; claims 15-23 are pending in this continuation application.

### Statutory Double Patenting Rejection

Claim 13 was rejected as claiming the same invention as that of claim 1 of prior U.S. Patent No. 5,547,994 and claim 14 was rejected as claiming the same invention of claim 1 of prior U.S. Patent No. 5, 362,755. To overcome this rejection, both claim 13 and claim 14 have been canceled by amendment above.

### Obvious-type Non-Statutory Double Patenting Rejection

Claims 13 and 15-22 were rejected as being unpatentable over claims 1-4 of prior U.S. Patent No. 5,547,994. Claims 14 and 15-22 were rejected as being unpatentable over claims 1-5 of prior U.S. Patent No. 5;362,755. Claim 23 was rejected as being unpatentable over claim 1 of prior U.S. Patent No. 5,547,994 and claim 1 of prior U.S. Patent No. 5,362,755.

In response to the above rejections, Applicants herewith submit Terminal Disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fee under 37 C.F.R. 1.20(d).

### Disclosure of Information under 37 CFR \$1.56

In the prosecution of parent case 08/335,480 (now US patent 5,547,994), applicants presented a Declaration under 37 CFR §1.132 by John R. McCullough. Dr. McCullough presented results of tests on airway smooth muscle cells that demonstrated unexpected differences among the enantiomers and racemate of albuterol on calcium mobilization and on

USSN 08/691,604 Barberich et al. Page -3

airways hyperreactivity. Following the presentation of this declaration and the accompanying response on January 22, 1996, the claims were allowed. Earlier in prosecution, on June 6, 1995, applicants had presented a Declaration under 37 CFR \$1.132 by Dean A. Handley showing the tremorogenicity of the enantiomers in mice. From the results in mice, Dr. Handley concluded that the use of the pure R enantiomer would result in less potential for tremorogenicity in humans. In the next Office Action following that declaration, the Examiner maintained the rejection and noted that the Handley declaration had been carefully considered, but it did not persuade the Examiner of error in his earlier rejection.

Subsequent to the prosecution of the '480 case, applicants have undertaken clinical trials in preparation for bringing the compositions and methods of the invention onto the market, including elimical trials directed toward determining tremorogenicity in humans. The results of the studies indicate that, notwithstanding the effects seen in the mouse tremorogenicity study, the S enantionner does not appear to be tremorogenic in humans. Applicants therefore do not believe it would be proper to rely on the declaration of Dr. Handley for patentability. Applicants present this information in order to satisfy their duty of disclosure, but they believe it has no practical effect on the patentability vel non of the claims, since the Examiner did not rely on the declaration of Dr. Handley for his determination of allowability. As regards the findings in the declaration of Dr. McCullough, on which the Examiner appears to have relied for allowance, Dr. McCullough remains comfortable with the results and conclusions presented in that declaration.



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There being no further outstanding issues, the application is believed in condition for allowance and such action is respectfully requested. However, should the Examiner have any further questions or comments regarding the pending claims, he is urged to contact Applicant's representative at the number below.

Respectfully submitted,

Philip E. Hansen

Agent for Applicants Reg. No. 32,700

Dated: Novaba 20, 1997 Hestin & Rothenberg, P.C. 5 Columbia Circle Albany, New York 12203 Telephone: (518) 452-5600 Facsimile: (518) 452-5579

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### SUBJECT: DECISION ON TERMINAL DISCLAIMENS INFORMAL FORM

1. Later.		
DATE: 12-15-97	APPL S.N.: 081 691 684	
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M. Montgomery ROOM 6618	MAILROOM DATE 11-24-97	
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Notice of Allowability

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12

Part of Paper No.

Page 11 of 33



UNITED STATES DÉPARTMENT OR COMMERCE -

### NOTICE OF ALLOWANCE AND ISSUE FEE DUE

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Case 1:06-cv-00113-JJF

APPLICATION NUMBER GROUP ART UNIT FILE WRAFFER LOCATION 08/691.604

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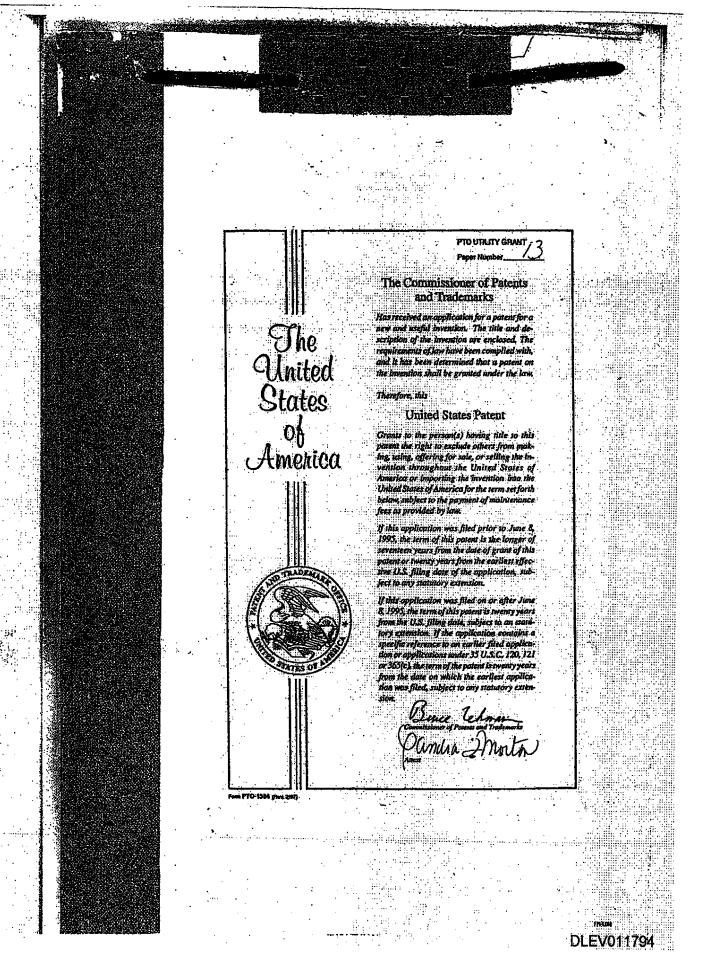
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DEUTSCHES PATENTAMT

- (3) Aktenzeichen:
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- (2) Anmeldetag:
- 7. 6.71 23, 12, 71
- Offenlegungstag:
- Veröffentlichungstag der Patenterteilung:

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- (1) Unionspriorität: (2) (3) (3)

  - 17,06.70 GB 29367-70
- (1) Patentinhaber.

Allen & Hanburys Ltd., London, GB

(4) Vertreter:

Jung, E., Dipl.-Chem. Dr.phil.; Schildewahn, J., Olpl.-Phys. Dr.rer.nat.; Pat.-Anw.; 3000 München @ Erfinder:

Middlemiss, David, London, GB

Im Prüfungsverfahren entgegengehaltene
 Druckschriften nach § 44 PaiG:

15 57 677

Verfahren zur Herstellung der optischen Enantiomeren von α¹-tent.-Butylaminomethyl-4-hydroxy-m-xyhlen-α¹:
 κα¹-diol, das R(-)-Enantiomete in Form des Hydrogenacetat-mohomethanol-Sötvets und Azznelmittel

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### Patentansprüche:

I. Verlahren zur Herstellung der optischen Enantiomeren von al-tert. Butylaminomethyl-4-hydroxy-m-xylylen-a'.a'-diol der Formel I

und ihrer Salze mit Shuren, dadurch gekennzeichnet, daß man einen basischen Ester der allgemeinen

in der R einen unverzweigten oder verzweigten Alkylrest mit I bis 6 Kohlenstoffatomen bedeutet, 25 mit einer optisch aktiven Form der Di-p-toluylweinsäure in einem organischen Lösungsmittel umsetzt, das entstandene Salz fraktioniert kristallisiert und die diastomeren Salze auftrennt, hieraus in üblicher Weise die Base in Freiheit setzt und diese in 10 beliebiger Reihenfolge reduziert und karalytisch entbenzyliert und gegebenenfalls die erhaltene Verbindung mit einer anorganischen oder organischen Säure in ein Salz überführt.

2 Verfahren nach Anspruch I, dadurch gekenn- 15 zeichnet, daß man die Umsetzung mit der optisch aktiven Form der Di-p-toluylweinsäure in einem Carbonsäurgester als Lösungsmittel durchführt.

3. Verfahren nach Anspruch 1 und 2. dadurch gekennzeichnet daß man die Reduktion mit 40. Lithiumaluminiumhydrid durchführt und zur katalytischen Entbenzyfferung einen Palladium-auf-Holz-kohle-Kalalysator verwender:

4. Verfahren nach Anspruch 1 bis 3, dadurch gekennzeichnet daß man das Verfahren, ausgehend von dem di-Racemat des 5-(2-Benzyl-tert-butylamino-1-hydroxy≩thyl)-2-benzyloxybenzoesäuremethylesters als basischem Ester der allgemeinen Formel II, durchlührt.

5. R(--)-Enantiomer von al-tert-Butylaminoāthyl-4-hydroxy-m-xylylen-a';x<sup>2</sup>-dlol-hydrogenacetai-monomethanol-Solvat

5. Arznelmittel, enthaltend das gemäß Anspruch 1 bis 4 hergestellte R(-)-Enantiomere oder dessen Saureadditionsssabe oder die Verbindung gemaß. Anspruch 5, als Wirkstoff.

Aus der FR-PS 15 57 677 sind Phenylaminoathanol-Derivate, wie at tert. Burylaminomethyl 4-hydroxy-mxylylen a za diol bekanna Diese Verbindungen können die B-Rezeptoren der adrenergenen Nerven stimulieren. 50 Diese Phenylaminoathanol Derivate können theoretisch in zwei optisch isomeren Formen vorliegen. Ebenso wie in Beispiel 16 der FR-PS 15 57 677 ist bisher nur die Raeematform der vorstehend genannten Verbindung beschrieben worden

Aufgabe der Erfindung war es daher, ein Verfahren zur Herstellung der optisch aktiven isomeren Formen (Enantiomeren) von a tert-Butylaminomethyl-4-hydroxy-m-xyfylen-a<sup>1</sup>cl<sup>1</sup>diot in möglichst reiner Form bereitzustellen. Diese Aufgabe wird durch die Erfindung 👸

gemäß den Patentansprüchen 1 bis 4 gelöst.

Weitere Gegenstände der Erfindung sind das

R(-) Enantiomere des æ-tert: Burylaminomethyl-4-hydroxy-m-xylylen-æl æl-diol-4-hydrogenacetat-monomethanol-Solvats gemäß Anspruch 5 sowie Arzneimitiel auf der Basis des durch das erfindungsgemäße Verfahren erhäldlichen R(-) Enanttomeren oder dessen Saureadditionssalzen oder des Hydrogenacetat-monomethanol-Solvats des vorgenamiten Diols, entsprechend Anspruch 5.

Das erfindungsgemäße Werfahren zur Herstellung der optischen Enantiomeren von altert-Butylaminomethyl 4 hydroxy m xylylen a 2-diol der Formel I

### 21 20 238

d ihrer pharmakologisch verträglich. Salze mit Säuren ist dadurch gekennzeichnet, daß man einen basischen ier der allgemeinen Formel II

ROOC
$$CH_{2}C_{4}H_{5}$$

$$C_{4}H_{5}-CH_{7}O$$

$$CH_{2}-CH_{2}-N$$

$$OH$$

$$tert_{2}-C_{4}H_{5}$$
(II)

der R einen unverzweigten oder verzweigten kylrest mit 1 bis 6 Kohlenstoffatomen bedeutet, mit der optisch aktiven Form der Di-p-toluylweinsäure in ihr organischen Lösungsmittel umsetzt, das entstange Market und die dastomeren 15 Balz fraktioniert kristallisiert und die dastomeren 15 Balz fraktioniert kristallisiert und die dastomeren 15 Balz fraktioniert kristallisiert und die Bass in beliebiger Reihenfolge fluziert und katalytisch entberzyliert und gegebenen ist die erhaltene Verbindung mit einer anorganischen und ein Salz überführt.

Die erfindungsgemäße Gewinnung der optischen tantiomeren unterscheidet sich von der in der FR-PS 17 677 angesprochenen üblichen Racumatspaltung durch, daß nicht das als Endprodukt gewünschte Diol her Freunbehandlung unterworfen wird, sondern eine 25 brstüfe in Form des basischen Esters gemäß Formel II. Auf diese Weise lassen sich die betreffenden haltiomeren in sehr reiner Form gewünnen, was bisher icht möglich war.

Diese Reinheit und die höhe pharmakologische in krivität spezielt des R(--)-Isomeren sind besonders ervoll für den Einsatz als Wirkstoff in Arzneimitteln. Die Reduktion wird z. B. mit einem Metallhydrid oder jomplexen Metallhydrid durchgeführt. Die Entberzylieting wird durch hydrierende Spaltung in Gegenwart stans ines Edelmetalkatalysators, wie Palladium, durchgelitt. Das Produkt kann als Salz mit einer Saure isoliert berden.

Die Isomeren haben in der Form des Acetat-Monohethanolats folgende physikalische Eigenschaften:

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Die Salze können sich von organischen oder anorganischen Säuren ableiten, wie Maleinsäure, Pumarsäure, Apleisäure, Bernsteinsäure, Essigsäure, Weinsäure, Balzsäure, Schweleisäure und Phosphorsäure.

Das R[-)-Isomer der Verbindung der Formel I wirkt 60 ils: Antagonist der erhöhten Bronchiafresistenz, die durch Verabfolgen von Acetylcholin an anästhesierte Meerschweinchen erzeugt wird (Konzett-Rössler-Präparat).

Daher betrifft die Erfindung auch Arzneimittel is entsprechend der oben gegebenen Definition, welche gegebenenfalls übliche pharmakologisch verträgliche Milissioffe und bzw. oder Trägerstoffe enthalten.

Beispiele für geeignete feste Trägerstoffe sind Maisstärke, Calciumsulfatdihydrar und Milchzucker,

Die Arzneimittel können entweder feste oder flüssige Präparate zur oralen Verabfölgung. Suppositorien, Injektionspräparate oder Inhalationspräparate sein. Präparate zur oralen Verabreichung liegen vorzugsweise in Form von Tabletten vor, die nach üblichen Verfahren hergestellt und gegebenenfalls dragiert sein, können Es kommen auch lösliche Sublingualtabletten in Frage.

Injektionspräparate können mit physiologisch verträglichen Trägerstoffen und Hilfsstoffen als Lösungen, Suspensionen oder als Trockenpräparate hergestellt werden die vor der Verwendung mit dem Verdünmungsmittel versetzt werden. Inhalationspräparate werden, vorzugsweise in Form von Aerosolspray-Präparaten hergestellt.

Die Beispiele erläutern die Erfindung.

### Beispiel 1

Spaltung von dt.5-(2-Benzyl-iert.buiyiamino-1-hydroxyäthyi)-2-benzyloxybenzoesäuremethylester und Unswandlung in die (+)- und (-)-lsomeren von al-tert-Buiyiaminomethyl-4-hydroxy-m-xylylen-al-al-diol

a)(-)5-(2-Benzyl-tert-butylamino-1hydroxyāthyl)-2-benzyloxybenzoesāuremethylester

Eine Lösung von 30 g der racemischen Base:—
hergestellt durch Kondensation von 2-Benzyloxy-5broniacetylbenzoesäuremethylester (vgl. J. Med. Chem.
Bd. 13 [1970] S. 674) mit tert-Batylbenzylamin in
Methyläthylketon und Reduktion des erbaltenen Produktes mit Natrumborhydrid in Äthanol nach dem in
der FR-Patentschrift 1557 577 beschriebenen Verfahren — und 25,6 g (+)-O,O-Di-p-tolopylweinsäure: in
350 ml. Äthylacetat. wird. auf 70°G erwärmt und
anschließend langsam auf Raumtemperatur abkühlen
gelassen. Das auskristallisierte Salz wird abfütriert und
getracknet: Ausbeure 27 g vom F 130,0°C, [2]? = 49°
[c=1; CHiOH). Nach dreimaliger Umkristallisation aus
Äthylacetat erhält man die Verbindung mit konstantem
Schmelzpunkt von 1425°C und konstantem Drehwert
[a]? = 47°C (c=12; CH<sub>2</sub>OH).

10 g des erhaltenen Salzes in Athylacetat werden mit wäßriger Natriumbicarbonatlösung behandelt. Die freie Base geht in die Äthylacetatphase übert während die Tohylweinsäure in die wäßrige Lösung übergeht. Die Athylacetatlösung wird eingedampft und der Rückstand aus Petroläther (Siedebereich 40 his 50°C) nmkristallisiert. Man erhält 3 g der freien Base in farblösen Nadeln vom F 87,0°C; [x] ? - 18,4° (c=0,38;CH<sub>3</sub>OH).

b)(+)-5-(2-Benzyl-tert-butylamino-1hydroxyāthyi)-2-benzyloxybenzoesāuremethylester

Diese Verbindung wird in Ahnlicher Weise wie

Document 274-12

vorstehend beschrieben mit (-)-O,O-Di-p-toluylweinsäure erhalten. Es werden 30 g der racemischen Base und 25,6 g (--)-O.Q-Di-p-tohylweinsäure in 350 ml Äthylacetat zur Umsetzung gebracht. Ausbeute 27 g des Salzes vom F 134 bis 135°C; [a] = -48° (c=1; CH3OH). Nach dreimaliger Umkristallisation aus Athylacetat hat das Salz einen konstanten Schmelzpunkt von 141,5°C und einen konstanten Drehwert [a]F von -47° (c=1.5; CH<sub>3</sub>OH).

F) g des erhaltenen Salzes in Äthylacetat werden mit 19 wäßriger Natriumbicarbonatlösung behandelt. Die in Freiheit gesetzte Base geht in die Athylacetatphase über, während die (-)-O,O-Di-p-toluylweinsäure in die wäßrige Lösung übergeht. Die Äthylacetatlösung wird eingedampit und der Rückstand aus Petroläther vom 15 Siedebereich 40 bis 60°C umkristallisiert. Man erhält 4.5 g der freien Base vom F87.0°C; [a]V = +18.3° (c=035; CH<sub>2</sub>OH):

### c) (+)-a1-tert-Butylaminomethyl-4-hydroxym-xylylen-a1 a1 diol-acetat

Eine Lösung von 2,5 g (--) 5-(2-Benzyl-tert-butylami-no-l-hydroxyāthyl) 2-benzyloxybenzoesāuremethylester in wasserfreiem Tetrahydrofuran wird innerhalb eines Zeitraumes von 5 Minuten in eine gerührte Lösung 25 von 0,5 g Lithiumaluminiumhydrid in 50 ml wasserfreiem Tetrahydrofuran eingetropft. Das Gemisch wird unter Rückiluß erhitzt und abkühlen gelassen. Anschlie-Bend wird nicht umgesetztes Lithiumaluminiumhydrid mit Wasser zersetzt und das Gemisch mit Ather so extrahiert Nach dem Eindampfen des Ätherextraktes hinterbleiben 2,1 g al-Benzyl-tert-butylaminomethyl-4-benzylöxy-m-xylylen-al-m²-diol als farbloses Ol. Das larblose Ol wird in 50 ml Athylacetat in Gegenwart von o.7 g 10prozentigem Palladium-auf-Holzkohle hydrient, 38 bis- die Wasserstoffaufnahme aufhört. Nach dem Abfiltrieren des Katalysators und Verdampfen des Lösungsmittels hinterbleibt (+)-al-tert-Butylaminomethyl-å-hydroxy-m-syhlen-alza-diol als farbloses Produkt; [a] 7 = +25° (c=0.4; CH-OH). Die freie Base 30 wird in das kristalline Acetat umgewandelt; das nach Umterstallissition aus Anst-Mitching von Meihangel und Umkristallisation aus tiner Mischung von Methanol und Ather bei 1430°C schmitzt; [a] = +36.9° (c=0.23; CHiOH) Dieses Salz kristallisiert mit 1 Mol Methaniol.

### d) (--)-x--tert.-Butylaminomethyl-4-hydroxym-xylylen-al-al-diol-acetat

Aul die in (c) beschriebene Weise wird der (+)-5-(2-Benzyl-tert, butylamino-1-hydroxyathyl)-2- 50 benzyloxybenzoesauremethylester mit Lithiumalumini-(c=0,36; CH3OH) Die freie Base wird in das Acetat 55 Oberführt und aus Methanol umkristallisiert. Das Acetat. kristallisiert mit 1 Mol Methanol und schmilzt bei 1433°C:[a]? = -369°(c=0.27;CH<sub>2</sub>OH).

Die nachstehenden Beispiele erläutern die Herstellung von Arzneipräparaten aus den optischen Enantio- 60 meren oder ihren Salzen, die gemäß Beispiel ! hergestellt wurden.

### Beispiel 2

Zur Herstellung von Tabletten werden die nachstehend aufgeführten Bestandteile in den angegebenen Mengen verwendet

Rezeptur	l mg Tublette	10 000 Tabletten
		· · ·
Arencistoff	1,2 mg	12,0 g
Calciumsulfat-dihydrat	88,2 mg	882,0 g
Maisstärke	24.0 mg	240.0 g
Modifizierte Stärke	6.0 mg	60,0 g
Magnesiumstearat	0.6 mg	6.0 g
i in the first of the second o	120.0 mg	1200,0 g

Die Tabletten werden folgendermaßen hergestellt:

- Sämtliche Bestandtelle, mit Ausnahme des Magnesiumstearats, werden miteinander vermiseht, das Pulvergemisch wird mit Wasser granullert und die leuchte Masse durch ein Sieb der lichten Maschen-
- weire 1,2 mm passiert:

  Das: feuchte Granulat wird getrocknet und anschließend durch ein Sieb der lichten Maschenweite 0.841 mm passieri:
  - Das getrocknete Granulat und das Magnesiumstearat werden hierauf miteinander vermischt und in einer Tablettiermaschine mit üblichen konkaven Stempeln mit einem Durchmesser von 6,35 mm zu Tabletten verpreßt.

### Beispiel 3

Zur Herstellung eines Aerosolpraparates werden die nachstehend genannten Bestandteile miteinander ver-

Rezeptur	100 ug Dosis
Arzneistoff	100 µg ,
Ölsäure	10 ng
Dichlordifluormethan Trichlorfluormethan	61 mg 24 mg

Der Arzneistoll, die Ölsäuse und ein Teil des Trichlorilliormethans werden miteinander vermischt. Anschließend wird die erhaltene Suspension mit dem restlichen Trichloritormethan verdünnt und in eine Sprühldose abgefüllt, die mit einem Dosiervenül verschlossen wird. Hierauf wird in die Sprühldose Dichlordilhormethan aufgepreßt.

### Beispiel 4

Zer Herstellung eines Aerosolpraparates werden dienachstehend genannten Verbindungen miteinander vermischt:

Rezeptur	100 µg Dosh
Arzneistoff	120 μg
Sorbittrioleat	120 µg
Dichlordiflyormethan	61 mg
Trichlorfluormethan	24 mg

Der Arzneistoff, das Sorbiturioleat und ein Teil des Trichlorsumethans werden miteinander vermischt. Hierauf wird die erhaltene Suspension mit dem ss restlichen Trichlorfluormethan verdünnt und in der erforderlichen Menge in eine Sprühdose abgefüllt, die mit einem Dosierventil versehen wird. Danach wird in die Sprühdose Dichlerdifluormethan aufgepreßt. 



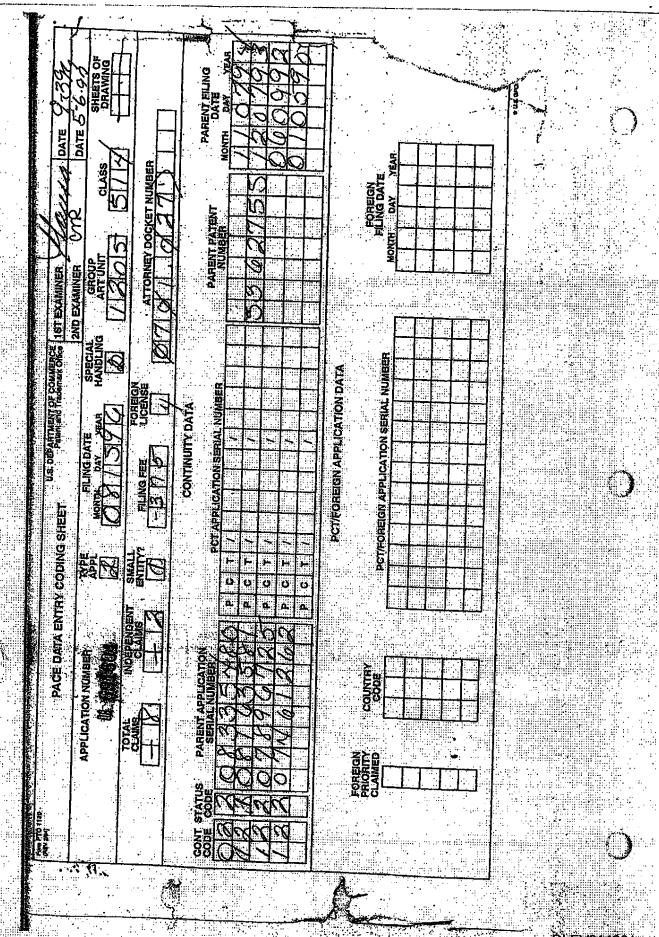
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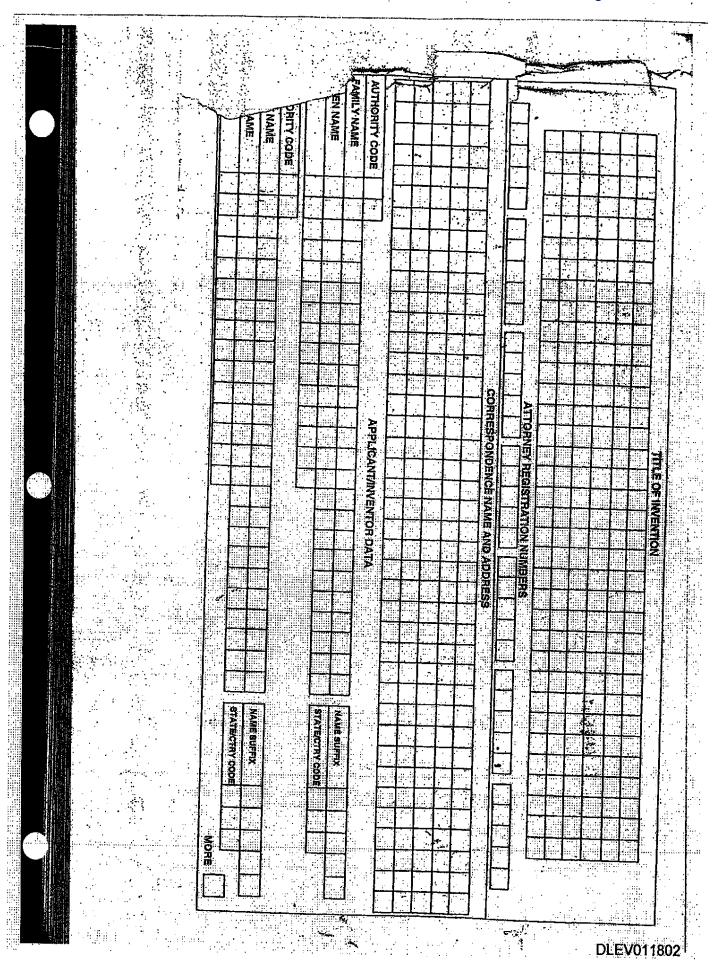
Zur Herstellung eines Aerosolpräparates werden die nachstehend genannten Bestandteile verwendet:

	Rezéplur	100,4g 1ksis	
	Arzneistoff 2-Dimethylaminosthanol Ötsäure Dichlordiffuormethan Trichlorsuormethan	120 µg 26,6 µg 93,4 µg 61 mg 24 mg	
Der Arzneistoff, die Obsaure nol und ein Teil des Trit miteinander vermischt. Hi	Pales Throngs a blood the state and the	verdünnt und die erford Sprühldose abgefüllt, die verschlossen wird Danach	lerliche Menge in mit einem Dosier
"Suspension mit dem rest	erau wro die ernaltene ichen Trichlorfbornethan	verschlossen wird. Danad Dichlordifloormethan aufger	i wird in die Sproi vreßt
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		ing to see the a hear grants in the c high parts in the co	
			an many repairs and a
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Der Arzneistoff, die Ölsäure, das 2-Dimethylaninoäthanol- und ein Teil des Trichkorfnormethans werden 15 Sprühlose abgefullt, die mit einem Dosterventilmitelnander vermischt. Ellerauf wird die erhaltene verschlossen wird Danach wird in die Sprühlose
Suspension mit dem restlichen Trichkorfnormethan Dichkordifnormethan aufgepreßt.

	PATENI	APPLIC	ATION F	E DETERMI October 1, 1995	NATION REC	ORD	Application			ei '
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	U.S. PATENT APPLICATION	
	SERIAL MUMBER CLASS GROUP ART UNIT	
	08/335,480 31/07/94 514 1205 RULB 60	
	TIMOTHY J. BARBERICH, CONCORD, MA; JAHES W. YOUNG, STILL RIVER, MA:	
	**CONTINUING DATA***********************************	
III E OF BUT MINON	**FOREIGN/PCT APPLICATIONS************************************	6
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	HETHOD FOR TREATING ASTEMA USING OPTICALLY PURE R(-) ALBUTEROL.	
	This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application which is identified above.	
	Dy and booking of the Commissioner of Patents and tradegoards	

# United States Patent [19] Patent Number: Barberich et al.

[54]	OPTIO	IOD I	OR V PO	TREA RE R	73年	STI	MA D	SHYG	
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- [75] Inventors: Timothy J. Barberich, Concord: James W. Young, Still River, hoth of Mass t grand the state of the state
- Assignee: Sepraeob, Inc., Mariborough, Mass.
- The farm of this patent shall not extend beyond the expiration date of Pa. No. 5.362,755. 10.74 100

Case 1:06-cv-00113-JJF

D11 April No. 691 664 [22] Filed: Aug. 15; 1996 Related U.S. Application Data:

# r. No. 335,480, Nov. 7, 1894, Par 180 a continued of Ser No. 143,481, Dec 16,255, Which is a continuation of Ser

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# U.S. PATENT DOCUMENTS

5392733 11/194 Besteich et 2 5547394 80396 Besteich et 2

5,760,090

1451 Date of Patent:

Hartley et al. "Absolute Configuration of the Optical Isomers of Sulbitanion" J. Med. Chem. 12, 993 [1971]. Hawkfar et al. Relative Potency is ("Praise(1) Substantial on Guines Pig. 1. Med. Chem. 16, 366-157 (1973).

CONTRACTOR SECTION TO THE PROPERTY.

Birthic & A. Stidles on the Effects of Rhantonics of Solerical Trinecognical . J. Phorm. Exp. Ther. 189. 616-625 (1974).

616-625 (1974).

Passowicz-Muszynska B. Effect on beta adrenergie 1900ptost-of tactisphylaxis — an index Medicus 91-160 28

Paragle, three of collections in the school of sin-pathonometrics. Index Medical, 36(5) 976. Regulations

Chapping A. L. An anomalous Creek of Survivined in sensitived groves page thru. J. Pharmagon 92, 505 (1990).

Algrey et al. "infects of (4) and raceing Labouring for anyth responses in the guines pig. Brit. J. Phyring of JUL 295P (1991).

(Application of al. "Racepule most tires at 1000 of worsening symptom? Active capationners ... "77PS 13, 251-252 

Muniteri et al. Comparison et scure pronincellans effects of gral salbatanol...... Chem. Aleste, 80: 123239m (1978).

The terms of the fact of Bringer, Empirer, Raymond Henley, III.
Amorney, Agent, or Firm Heslin & Rothenberg, P.C.

[57] ABSTRACT

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Page 26 of 33

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### METHOD FOR TREATING ASTRINA USING OPTICALLY FURE R(-) ALBUTEROL

Document 274-12

This is a continuation of U.S. application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547, 994, which is a continuation of U.S. application Set. No. 08/16/5,581 filed Dec. 7, 1993, now U.S. Pat. No. 5362,755, which is a continuation of U.S. application Ser. No. 07/896. 725, filed Jun. 9, 1992, abandoned, which is a continuation of U.S. application Sec. No. 07/461/262; filed Jan. 5, 1990, abandoned.

### BACKGROUND

Albulated is a drug belonging to the general class of beta-advenergic compounds. The prime action of betabeta-adivisorgic compounds. The prime action of betaadracegic drugs is to stimulate adenyl cyclase, the enzyme
which catilyzes the formation of cyclic-15 adenosine
monophosphate (AMP) from adenosine in phosphate (ATP).
The cyclic AMP formed mediates the cellular responses.
Albelical acts selectively on beta-adrencype receptors to
relax smooth multile fissue, for example, in the bronchial
system, absociated with ashima and is the active component
in well-known commercial bronchodilators such as Proyentil and Ventolin. til and Ventolini

The form in which albuterol is presently used is a recentle infrative. That is, it is a mixture of optical isomers, called enautioners. Resultences are structurally identical core. pounds which differ only in that one former is a mirror image of the other and the mirror images ramnot be super-imposed. Thus phenomenon is known as chirality. Most taclogical molecules exist as enautioners and exhibit chirality. Although structurally identical, enautioners can have hy. Among structurally recement, communicate can have profoundly different effects in biological systems: one commissioner may have a specific biological activity while the other enablesmen has no biological activity at all, or may have an entirely different form of biological activity.

### SUMMARY OF THE INVENTION

"The present devention relates to a method of treating broachthi disorders, such as autima, in an individual, py administrating, to the individual an amount of optically pure R(-) alternal which is active in proaching fassic sufficient to reduce throaching species associated with astima while minimizing side effects associated with alternal. The majorital presiduality useful in treating actions while retinoling side effects, such as council nervous system attinuistory effects and cardial arrestonic to these arcolications, it is effects and cutilian anythmiss in these applications, it is important to have a composition which is a potent broacho-dilator and which does not exhibit the advesse aids affects of many beta adrenergie drugs. A composition containing the pure R(-) isomer of albuterol is particularly asciul for this application because this isomer exhibits these desired that 50 acteristics. The present method provides a safe, effective method for treating asthma while reducing indestrable side effects, for example, tremor, nervousness; shakiness; dizzl-aces and increased appetite, and particularly, cardiac arrythmia, typically associated with beta adrenerple drugs: In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure farmer is administered. In addition to the above, at certain levels recemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure 60 isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

### DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho dilation activity of the R(-) enantioner of albaterol to provide relief from

broachial disputers, while simultaneolisty feducing machina able side effects, for example, central nervous system stime able side effects, for example, central nervous system summ-latory effects and cardiac disorders, companyly experienced by allowed laters, in the present method, the optically time R(+) isomer of allowed, which is substantially free of the S(+) enantomer, is administered alone, or in combination with one of filter other trades) in significative transition, to an individual in whom assimir relief (etc., relief from broaching spesies, shortness of breath) is desired. The optically pure R(-) isomer of albeterpl as used herein refers to the levero-tatory optically pure isomer of α ((thi butylamino) methyl). 4-hydroxy, poxyleno to odiol, and to any biologically acceptable salt or estar increof. The leging "optically pure of "substantially free of the S(+) entailedner," as used berein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer Optically plus albuterol of readily obtainable by methods knows to those of adult in the artefor example, by synthesis from an optically pure intermediate.

In the present muchod, the R(+) isomerciof albertal is administered to an individual who has astima. For example, R(-) albuterol is administered to an individual afterouser of a sthma to reduce in cashing difficulty resulting dividual astum astum in another tembership optically price R(-) albuterol is administered prophylactically, that is, before, the tronchiospann begins in an asthma attack, to prevent its occur-rence of to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be a diministered by inhalation, by subcutaneous or bilier injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administrated (e.g. labelen, powder, tablet, capsule, solution, condition) will depend on the foute by which it is administrated. The quantity of the 35 drug to be administrated will be determined on an individual. dring to be administered war or occurrence on an marrowant basis, and will be haved at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought in general, quintities of optically pure R(-) allustrool sufficient to reduce the symptoms of artima will be administered. The active dought (quantity administrated at a time) and the number of admin-istrations per day will depend on the mode of administration. for consuple, by intake, actualists or oral administration.

About 30 mcg to about 90 mcg of the optically pass R4-)

istinct of altertol given by inhibitor one or more times
per day will be adequate in most individuals to predict the
desired branchedilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 2 mg two to four times daily is administered to produce the desired elfect.

In the method of the present invention, the optically pure R(-) isomer of albutcool can be administered together with one or more other drug(s). For example, an autiastimatic drug such as theophylline or terbutaline, or an antihistamine SS or analgesic such as aspirin, acetaminophen or ibuprofes, can be given with or in close temporal preximity to administration of optically pure, R(-) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two reparate entition For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure abouted and another drug or drugs, are determined primarily by the 65 manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or

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propellient. A composition to be administered in tablet form can include a filler (e.g., lactost), a blader (e.g., carboxym-ethyl cellulose, gum arabic, grlatin), an adjavant, a flavoring agent, a coloring agent and a coating material (e.g. wax o a plasticizer). A composition to be administered in liquid form can include the combination of drogs and, optionally, an combination agent, a flavoring agent and/or a coloring

In general, according to the method of the present invention, the optically pure R(-) isomer of albertroi, alone  $^{10}$ or in combination with another drug(s), is administered to an individual periodically as accessary to notice symptoms of

The present composition and method provide an effective transmit for autima while minimizing the understable side effects associated with albuterol use. These side effects include central nervous system effects, such as frames, nervousness, shakiness, dizziness and increased appetite, and cardise effects, such as cardise anythings. In children, side effects, such as excitement, nerrousness and hyperkinesia; are reduced when the part isomer is admin-istered. In addition, it adopting effects: associated with albeterol are believed to reside in the S(+) enumioner. Thus, administering the pure R(-) isomer may reduce the terato-genic potential associated with albuterol.

# **EQUIVALENTS**

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention

described hearth. Such equivalents are intended to encompassed in the scope of the following claims:

the compassion in the scope of the following change.

We claim:

L. A method of intaking astimas, while reducing side effects associated with the administration of resemble albaterol, comprising administering to an individual stiffering from astimas a quantity of an optically pure R(-) isomer of albaterol sufficient to result in proschodilistics while simultaneously reducing undestrable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method according to claim 1, wherein the albuterol

2. A method according to claim 1, whereis he abouterof computers at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, whereis the albuterol computes at least 90% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, whereis the optically pure R(-) albuterol is administered by labelation.

5. A method according to claim 3, whereis the ootleally

5, A incited according to claim 4, wherein the optically pure R(-) albutered is administered in an amount of about 30

ug to about 90 µg.

6. A method according to claim 1, wherein the optically pure R(-) altouerol is administered orally.

A method according to claim 6, wherein the optically pure R(-) albutered is administered in an amount of about 1

pint of -/ applicable seminateriol in an amplitude about 3 mg.

8. A method according to claim 6; wherein the optically pint R(-) albuterol is administrated as a syrup.

9. A method according to claim 7, wherein the optically

9. A misthod according to claim 7; wherein the symmatry pure R(-) albutered is subministered as a symily.

# United States Patent [19] Barberich et al.

[11] Patent Number: [45] Date of Patent: 5,547,994

Aug. 20, 1996

[54] METHOD FOR TERATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL.

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of

[73] Assigner: Sepracor, Inc., Mariborough, Mass.

[21] Appl No.: 335,480

[22] Filed: Nov. 7, 1994

Related U.S. Application Data

Continuation of Ser. No. 183,581, Dec. 7, 1933, 2nd No. 5,562,753, which is a continuation of Ser. No. 896,725, Jun. 5, 1992, charactered, which is in continuation of Ser. No. 461,262, Jun. 5, 1990, abundanced.

[51] Int. Ct.\* [52] U.S. Ct. U.S. CL 514/649; 514/826 [58] Held of Search

(56)

References Cited

U.S. PATENT DOCUMENTS

5,362,755 11/1994 Barbarich et al. \_\_\_\_\_ 514/649

POREIGN PATENT DOCUMENTS

2255503 7/1992 United Kingdom

OTHER PUBLICATIONS

Tan et al. "Stereis-lective Disposition of Salbutamoi Husn-Homers ... Clin. Chem. 33, 1026 (1987). Brittein et al. "Some observations on the β-adm agonist ... " Br. J. Fharmac. 48, 144-147 (1973).

Hartley et al. "Absolute Configuration of the Optical Isomers of Salbutano?" J. Med. Chem. 12, 995 (1971).
Hardeline et al. "Reinitive Entercy of (-) and (2). Salbutanol on Guines Pig..." J. Med. Chem. 16, 858–857 (1979).
Brokner et al. "Stodies on the Effects of Enumerous of Sources of Thinkbourful..." J. Phartn. Exp. Ther. 189, 616–625 (1974). 616-625 (1974).

616-625 (1974): Passowicz-Mussynska P. "Effect on beta aftenergie recep-tura of tactifythylaxia". "Index Medicus 91:164287 (1990).

Parweis "Riftet of civileosiscolids on the action of symposison and the state of civileosiscolids on the action of symposison in the state of the state of \$1.000 (1985).

Chapman et al. "An atomistous effect of calbitantial in sensitied prints pigs" Brit. J. Pharmacol 99, 667 (1990).

Markey et al. "Riftets of (+) and meanine salbutaned on all way responses in the guines pig" Brit. J. Pharmacol. 104, 2557 (1991).

Companies at "Execute intrins at root of worsening symptoms? Active confidences : . " The 11, 231-232 (1992).

Minimal et al. "Comparison of score bronchedilator effects of enal salbationed...." Client Abort 89: 123259m (1978).

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ABSTRACT .

The optically pure R(+) horner of abserved, which is sob-stantially free of the S(+) isomer, is a potent branchofflator for relieving the symptoms associated with asthma in indi-viduals. A method is of solessed satilizing the optically pure R(+) isomer of abserved for meating asthma while module-ing the side effects associated with abserved.

6 Claims, No Drawings

Case 1:06-cv-00113-JJF

### METHOD FOR TRRATING ASTHMA USING OFFICALLY PURE R(-) ALBUTEROL

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/163-581, filed Dec. 7, 1993 and now U.S. Pat. No. 5,362,755, which was a configuation of application Ser. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Ser. No. 07/461,282 filed Jan. 5, 1990, now absordenced.

### BACKGROUND

Albuterol is a drug belonging to the general class of 15 bets adventually compounds. The prime action of bets adventually compounds and prime action of bets adventually drugs is to stimulate adenyi cyclase, the croping which catalyzes the formation of cyclio-3.5-actionsine manuplanephase (AMP) from advancing triplocophiese (ATP). The cyclic AMP formed mediates the religious receptors to relat smooth acceptors to that amounts muscle thesise, for example, in the branchial system. Albuterol is must commonly used mitters becaused in system. Albuterol is most commonly used to treat bronchild spasms associated with authora and is the active component in well-known commercial broughodilators such as Proven- 25 til and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, eatled continuers. Ensettomers are structurally identical compounds which differ only in that one Boner is a mirror mage of the other and the mirror images campot be superimage of the outer and the mirror images caupet the super-imposed. This phenomenon is known as chirality. Most biological molecules exist as constituted and exhibit chiral-ity. Although americally identical, emantioners can have profoundly different effects in biological systems: one cann-tioner may have a specific biological activity while the other canniforms has no biological activity at all, or may have an entirely different form of biological activity.

### SUMMARY OF THE INVENTION.

The present invention relates to a method of treating bronchiel disorders, such as asthma, in an individual, by administrating to the individual an amount of optically pure R(-) albuterol which is active in besochial tissue sufficient 45 to reduce broughlat speams associated with asthma while minimizing side effects associated with allmerol. The method is particularly useful in treating asthma while reduc-ing side effects, such as control nervous system stimulating effects and cardiac arrythmia. In these applications, it is so impletant to have a composition which is a potent breachodilator and which does not exhibit the adverse side effects of many beta-adrenciple drugs. A composition containing the pure R(-) isomer of albeterol is particularly useful for this application because this isomer exhibits these debited class- 55 acteristics. The present method provides a safe, effective ethod for beating asthma while reducing undericable side effects, for example, tremor, nervousness, shakmess, dizziness and increased appetite, and particularly, cardiac arryth-mla, typically associated with beta siftenergic drugs. In so children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure issues is administered. In addition to the above, at certain levels recemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure 63 isomer reduces the teratogenic potential which is associated with the S(+) isomer of albumot.

### DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncheditation activhy of the R(-) cusationner of albeterol to movide pilef from intenchial disorders, while simultaneously reducing undesignable side effects, for example, octaval nervous system simullatory effects and cardino disorders, commonly especiment by albutated users. In the present method, the optically pure R(-) isomer of althresol, which is substantially five of the S(+) countioner, is administered since, or in committee with one or more other thing(s) in adjunctive treatment, to an S(1) communate with cost of the child of the cost of the cost of the child of the c spanna, shortness of herath) is desired. The optically pure R(-) isomet of albeiterol as used bestin refers to the levero-interly optically pure isomet of al (next-butylamino) methyll—4-hydroxy—xylane;a; of-diol, and its any biologically acceptable albor estet lucted. The terms "optically pure" to "authorism in the resist lucted. The terms "optically pure" to "authorism is much between means that the composition contains at least 90% by weight of the R(-) isomet of albeiterol and 10% by weight or less of the S(+) isomet. Optically pure albeiterol it resultly obtainable by methods known to those of altill in the set, for examina, he evaluated from an ordically tang interpolation. example, by synthesis from an optically pure intermediate.

example, by synthesis man an optically once increases.

In the present method, the R(-) issues of allowers is administered to an individual who has assiman. For example, R(-) allowers is administered to an individual after once of assimat to reduce breaking difficulty resulting from authoria. In mother embodiment, optically pure R(-) allowers is administered prophylactically, that is, before the both chlospann begins in an asthma attack, to prevent its occurrence on to orders the extent in which it prepays. chospan reguls in an assume man, it presents

In the present method, R(-) albustud can be whiteinstreed by inhabition, by subscataneous or other injection, orally, inhabition, by subscataneous or other injection, orally, inhabition, by subscataneous or other injection, orally, inhabition, by subscatally, percentally, transformally, seemlly or via an implanted reservoir constaining the drug. The furning which the drug will be administred (e.g., inhabitat, powder; subjet, capsule, solution, emulsion) will depend out the roots by which it is administered. The quantity of the drug to be administered will be returned on an individual limits and will be heard of less to receive and will be heard of less to receive and will be heard of less to receive and of less than the proof of less to receive the second of less than the proof of less to receive the second of less than the proof of less basis, and will be based at least in part on consideration of the ludividual's size, the severity of the symptoms to be mented and the result sought. In general, quantities of optically pure K(-) albuterol sufficient to reduce the symp-toms of astuma will be administrated. The actual dosage (quantity schemattered at a time) and the number of simunistrations per day will depend on the mode of administration. for example, by inhaler, nebulizer or bral administration. About 30 mcg to about 90 mcg of the optically pure R(-) home: of allinterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tables or symp, a dose of about I mg to about 8 mg two to four times daily is administered to produce the desired

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an amissibiratio one in three dust unigns, for example, an amissionance drug stell as theophylline or terbuthline, or an antihistamine or analgesic such as aspirine, acctanding place or the professional station of optically pure, R(-) albaterol. The two (or more) drugs (the optically pure active isomer of albaterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a par-

ticular composition, in addition to optically pure albaterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For crample, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form propellent. A compession to be auminatoric in major roma can incline; a filter (e.g., lactose), a binder (e.g., carboxymethy) cribulose, gam arabic, gelatio), an adjuvant, a flavoring agent, a coloring agent mad a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid to found can include the combination of drugs and, optionally, att contrifying agent, a flavoring agent and/or a coluting

In general, according to the method of the present inve tion, the optically pure R(-) isomer of aboverof, alone or in 15 combination with another drug(s), is administrated to an individual periodically as necessary to reduce symptoms of

The present composition and method provide an effective resument for authors while minimizing the andextrable side effects associated with albuscult use. These side effects include central network system offects, such as seemed pretite, and cardino affects, such as candine anythmia. In children, side effects, such as excitement, nervousness and hypertheoretic and cardino affects; such as cardine anythmia. In children, side effects, such as excitement, nervousness and hypertheoretic, are reduced when the pure isomer is administered. In addition, terratography effects associated with albuscult are helieved to reside in the S(+) examinance. Thus, administering the pure R(-) isomer may reduce the terratograph potential associated with albuscult.

EQUIVALENTS

described berein. Such equivalents are intended to be encompassed in the scope of the following claims. We claim:

1. A method of meating an acute attack of exilma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administring to an individual sufficing from an acute attack of asilium a quantity of an optically pure R(-) isomer of allustric inflicions to result in hunchodization while simultaneously reducing underhable side effects, said R isomer being substantially free of its 5(+) isomer.

ee of its S(t) isomer. 2. A method of claim 1 wherein the amount of the R(-) isomer of abolem is greater than approximately 90% by weight.

weigh;
3. A method of claim 2 wherein the amount of the R(-) framer of abstract its greater than 99% by weight.
4. A method of claim 1 comprising administering to the individual by inhelicitor from approximately 30 mag is approximately 90 mag of the R(-) isomer of albuticity per

 S. A method of treating an acuse attack of subma, winter reducing sale effects associated with the acuse administra-tion of raccasis albutatol, comprising administrator to any tion of measure about not, comprising administering in an analyticual sufficient from any scatt attack of submit a quintity of an optically, pure R(-) isomer of about rot multicless to result in proceducitation while simultaneously producing undestrable side effects, and at least one additional drug selected from the group constating of breached listons, partitionances and analysiss.

6. A method of chain 5 whereis the analysis is selected from the source multiples as assisted a section and the source constating of the subjects is selected. ACCUPATIONS

These shilled in the set will cognite, or be shill to section, judge a word has not since experimentation, making of specific shill be shilled in the set will cognite, or be shill to section, judge a word has not since experimentation for the group form of specific shill be shill be shill be shill be shilled in the set will cognite, or be shill to section, judge as well as possible consolidation of the investion.

\*\*A method of chain 5 where the benefits in substant and shill be s

